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[54] NITRIC OXIDE SYNTHASE INHIBITORS

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Related U.S. Application Data

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| | doned. | | | | | | | | |

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| [52] | U.S. Cl | 514/564 ; 514/565 |
| [58] | Field of Search | 514/564, 565 |

[56] References Cited

U.S. PATENT DOCUMENTS

| 4,282,217 | 8/1981 | Baglioni et al 424/240 |
|-----------|---------|------------------------|
| 5,028,627 | 7/1991 | Kilbourn et al 514/565 |
| 5,081,148 | 1/1992 | Braquet et al 514/162 |
| 5,158,883 | 10/1992 | Griffith 435/240.2 |
| 5,356,873 | 10/1994 | Mark et al 514/2 |

FOREIGN PATENT DOCUMENTS

A10230037 7/1987 European Pat. Off. .

WO91/04023 4/1991 WIPO .

WO93/00893 1/1993 WIPO .

OTHER PUBLICATIONS

CA 118:78331, Nava et al., 1992.

Tissue injury caused by depostion of immune complexes is L-arginine dependent; vol. 88 pp. 6338-6342, Jul. 1991; Medical Sciences; Michael S. Mulligan et al.

Beckman, J. S. The double-edged role of nitric oxide in brain function and superoxide-mediated injury. J. Dev. Physiol. (Eynsham). 15: 53-60, 1991.

Li, L. et al. Role of nitric oxide lysis of tumor cells by cytokine–activated endothlial cells. Cancer Res. 51: 2531–2535, 1991.

Nakaki, T. et al. Inhibition by nitric oxide and nitric oxide–producing vasodilators of DNA synthesis in vascular smooth muscle cells, Eur. J. Pharmacol. Mol. Pharmacol. Sect. 3: 347–353, 1990.

Boughton Smith, N. K. et al. Protective effect of S-nitroso-N-acetyl-penicillamine in endotoxin-induced acute intestinal damage in the rat. Eur. J. Pharmacol. 191: 485-488, 1990.

Hutcheson, I. R. et al. Role of nitric oxide in maintaining vascular integrity in endotoxin-induced acute intestinal damage in the rat. Br. J. Pharmacol. 101: 815–820, 1990.

Kilbourn, R. G. et al. Reversal of Endotoxin–mediated shock by N^G –methyl–L–arginine, an inhibitor of nitric oxide synthesis. Biochem. Biophys. Res. Comm. 172(3): 1132–1138, 1990.

Marshall, J. J. et al. Endothelium-derived relaxing factors. A perspective from in vivo data. Hypertension 16: 371–386, 1990.

Rubanyi, G. M. et al. Cytoprotective function of nitric oxide inactivation of superoxide radicals produced by human leukocytes. Biochem. Biophys. Res. Commun. 181: 1392–1397, 1991.

Palmer, R. M. J. et al. The role of ntric oxide in endothelial cell damage and its inhibition by glucocorticoids. Br. J. Pharmacol. 105: 11–12, 1992.

Wright, C. E. et al. Protective and pathological roles of nitric oxide in endotoxin shock. Cardiovasc. Res. 26: 48–57, 1992. Ialenti, A. et al. Modulation of acute inflammation by endogenous nitric oxide. Eur. J. Pharmacol. 211: 177–182, 1992.

Bergmann, L. et al. Cytotoxic action of IL-1B against pancreatic islets is mediated via nitric oxide formation and is inhibited by N^G-monomethyl-L-arginine. Febs (Fed. Eur. Biochem. Soc.). Lett. 299: 103-106, 1992.

Langrehr, J. M. et al. Evidence that nitric oxide production by in–vivo allosensitized cells inhibits the development of allospecific CTL. Transplantation (Baltimore) 53:632–640, 1992.

Demerle Pallardy, C. et al. Absence of implication of L-arginine/nitric oxide pathway on neuronal cell injury induced by L-glutamate or hypoxia. Biochem. Biophys. Res. Commun. 181: 456–464, 1991.

Billiar, T. R. et al. Modulation of nitrogen oxide synthesis in vivo: N^G -monomethyl-L-arginine inhibits endotoxin-induced nitrite/nitrate biosynthesis while promoting hepatic damage. J. Leuk. Biol. 48: 565–569, 1990.

Ochoa, J. B. et all. Nitrogen oxide levels in patients after trauma and during sepsis. Ann. Surg. 214: 621–626, 1991. Bone, R. C. The pathogenesis of sepsis. Ann. Intern. Med. 115:457–469, 1991.

Dal Nogare, A. R. Septic shock. Am. J. Med. Sci. 302: 50-65, 1991.

Nava, E. et al. The role of nitric of nitric oxide in endotoxic shock. (Corresponds to the poster). (1991).

Rees, D. D. et al. A specific inhibitor of nitric oxide formation from L-arginine attenuates endothelium-dependent relaxation. Br. J. Pharmacol. 96: 418-424, 1989.

Sakuma, I. et al. Identification of arginine as a precursor of endothlium-derived relaxing factor. Proc. Natl. Acad. Sci. USA. 85: 8664–8667, 1988.

Beckman, J. S. et al. Apparent hydroxyl radical production by peroxynitrite: Implications for endothelial injury from nitric oxide and superoxide. Proc. Natl. Acad. Sci. USA. 87: 1620–1624, 1990.

Beckman, J. S. Ischaemic injury mediator. Nature 345: 27–28, 1990.

(List continued on next page.)

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[57] ABSTRACT

The present invention discloses a method for inhibiting tissue damage in mammals caused by pathological NO production, which comprises administering an effective tissue damage inhibition amount of a NO synthase inhibitor to said mammal. Preferably the NO synthase inhibitor is L-NMMA.

8 Claims, 3 Drawing Sheets